

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

LINDA A. WATTERS, Commissioner, Offices :
of Financial and Insurance Services for the State :
of Michigan in her capacity as Rehabilitator of :
The Wellness Plan and in her capacity as :
Liquidator of Michigan Health Maintenance :
Organization Plans, Inc., formerly known as :
OmniCare Health Plan, Inc., individually and on :
behalf of all others similarly situated, :

Plaintiff, :

v. :

ASTRAZENECA PHARMACEUTICALS LP, :
and ZENECA, INC., :

Defendants.

Civil Action No.

CLASS ACTION COMPLAINT

JURY TRIAL DEMANDED

CLASS ACTION COMPLAINT

Plaintiff alleges upon personal knowledge and belief as to her own acts, and upon information and belief (based on the investigation of counsel) as to all other matters, as to which allegations Plaintiff believes substantial evidentiary support will exist after a reasonable opportunity for further investigation and discovery, on behalf of all others similarly situated, as follows:

I. NATURE OF THE ACTION

1. AstraZeneca Pharmaceuticals LP and Zeneca, Inc. ("AstraZeneca") had a patent for the drug Prilosec which by the year 2000 was the most widely prescribed drug in the world. Prilosec is a proton-pump-inhibitor ("PPI") or acid pump inhibitor that is used to treat heartburn. Prilosec is comprised of an organic molecule, omeprazole, which – like most organic molecules – exists in two forms (or "isomers") that are mirror images of each other. Prilosec is what is

called a “racemic” formulation of this molecule, meaning that it is comprised of a mixture of both mirror images (so-called “S” and “R”) of this molecule. By 2000, sales of Prilosec had reached \$6 billion, making it the top selling drug in the world in terms of sales.

2. A patented drug is also referred to as a “brand name” drug. Brand name drugs which face no competition are the most profitable drugs for drug manufacturers. In the year 2000, the average retail price of a prescription drug was more than three times that of a generic drug.¹

3. The patent for Prilosec was set to expire in 2001 and AstraZeneca anticipated that it would face stiff competition from generic manufacturers. It is a fact well known to drug manufacturers that entry of generics results in a substantial loss of market share, sharply reduced prices, and a decrease in profits. AstraZeneca was facing the loss of its most profitable drug.

4. Within AstraZeneca, a group of marketers, lawyers and scientists was formed to come up with a solution for what the company believed was a looming patent-expiration disaster. The group called itself the “Shark Fin Project” after the dismal shape the sales chart would trace if they did nothing: an inverted V. In response, AstraZeneca launched a multi-prong attack. First, it attacked generic manufacturers in court seeking to delay entry of competition. Second, shortly before the patent on Prilosec was set to expire, the company got FDA approval for the newly patented Nexium. Then it launched a massive advertising campaign to persuade Prilosec users and their doctors that Nexium was somehow better. Very quickly, Nexium became the most heavily advertised drug in the United States. The media was blanketed with Nexium ads – “Today’s purple pill is Nexium, from the makers of Prilosec.” To help with the switch, AstraZeneca originally priced Nexium below Prilosec, gave discounts to managed care plans and hospitals, barraged doctors with free samples, and even offered coupons in newspapers. AstraZeneca’s 6,000 salespeople barraged doctors with studies proclaiming Nexium’s superiority. The promotional campaign reportedly cost the company a half billion dollars in just

¹ *Trends as Indicators in the Charges*, Health Care Marketplace 2004 Update, Kaiser Family Foundation.

2001. Virtually overnight, Nexium – the new purple pill – began to replace Prilosec. Soon the company dropped all references to the older drug, Prilosec, in its advertisements. Now they just refer to “the purple pill called Nexium.” It is as though Prilosec never happened. (In fact, Prilosec is now sold over the counter for a fraction of the cost of Nexium, Prilosec sells at \$0.46 per pill and Nexium at over \$4.00 per pill.)

5. To get FDA approval for Nexium, AstraZeneca had to test it in several clinical trials. Some of these trials merely compared Nexium with placebos to show that it worked better than nothing, since that is all the FDA requires. But four trials, compared Nexium head to head with Prilosec (for esophageal erosions), and these were crucial to the marketing strategy. The company wanted to show that Nexium was better than Prilosec – an advance over the older drug.

6. Instead of comparing equivalent doses, which would have been 20 mg of Nexium, versus the standard 20-milligram dose of Prilosec (the dose recommended for most indications – duodenal ulcer, erosive esophagitis, and GERD), the company included higher doses of Nexium in its studies. Four studies were performed by AstraZeneca comparing Nexium 40 mg to Prilosec 20 mg. With the dice loaded in that way, Nexium looked like an improvement – but still only marginally so and in just two of the four trials.² In fact, the only surprise is that at the high doses chosen for comparison, Nexium didn’t do better than Prilosec did. Two studies compared equivalent 20 mg doses of Nexium and Prilosec. In one, patients with endoscopy confirmed esophagitis treated with Nexium were 3% more likely to have healed after eight weeks of therapy with Nexium, (89.9% vs. 86.9%). In practical terms this meant that patients taking Nexium 20 mg appreciated symptom relief in 7-8 days, whereas those who took Prilosec 20 mg improved in 7-9 days. But even the miniscule benefit was neutralized by the 3.1% greater incidence of the most common side effects including headache, abdominal pain, and diarrhea that occurred in the people taking Nexium (though this total was not tallied in the article

² Gardiner Harris, *AstraZeneca Fends Off Generics for Prilosec ---- New Heartburn Drug Nexium Is Introduced*, WALL STREET JOURNAL, June 6, 2002.

presenting the results of this study).³ Furthermore, if there were a necessity to improve therapeutic efficacy beyond that provided by Prilosec 20 mg, the logical approach would have been simply to double the standard dose of Prilosec, allow generic competition, and forget about Nexium – but that would not have been of help to the profit-making objective of AstraZeneca.

7. Instead, based on the flawed trial comparing 40 mg of Nexium to 20 mg of Prilosec, AstraZeneca promoted Nexium to doctors and consumers as the “first proton pump inhibitor (PPI) to offer significant clinic improvements over Losec and its main competitor, lansoprazole, in terms of acid control and clinical efficacy.”⁴ It also claimed that Nexium was more effective in acid inhibition than other comparable drugs and provided relief in a shorter period of time. AstraZeneca repeated this message in a barrage of marketing activities directed to patients and doctors. For example, at the Pri-Med primary care continuing medical education conference held in Boston in October 2004, one of the largest in the country, AstraZeneca representatives engaged physicians in discussions about Nexium and encouraged doctors to take their marketing material. The back cover of one pamphlet is headlined “Acid Protection THE NEXIUM DIFFERENCE.” The graph presents the results of a study showing that Nexium 40 mg. maintains gastric acid suppression (gastric pH>4) for 14.0 hours compared to, among other drugs, Prilosec 20 mg, which only maintained gastric pH at this level for 11.8 hours. To a trusting doctor attending the conference, this might appear to be a convincing advantage of Nexium 40 mg and the basis of his or her decision to prescribe this drug at this dose for patients. The problem is, however, that the results of another AstraZeneca-sponsored study showed the clinical irrelevance of this data about stomach pH – at least for many patients. This study – accepted for publication seven months *before* the marketing material was handed out at the Pri-Med conference – showed that there was absolutely no advantage to Nexium 20 or 40 mg over

³ Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole Improves Healing and Symptom Resolution as Compared with Omeprazole in Reflux Oesophagitis Patients : A Randomized Controlled Trial. The Esomeprazole Study Investigators. *Alimentary Pharmacology & Therapeutics*. 2000; 14(10):1249-1258.

⁴ AstraZeneca Annual Report Form 20-F-2000 at p. 11.

Prilosec 20 mg for patients with “endoscopy-negative reflux disease” (a large percentage of the patients for whom Nexium is prescribed):

“Conclusions: More than 60% of endoscopy-negative reflux disease patients reported heartburn resolution, but, after 4 weeks of therapy, these proportions did not differ significantly between treatments [Nexium 20 mg, Nexium 40 mg, and Prilosec 20 mg].”⁵

8. The attendees of the conference were, therefore, left unaware that their patients would get equivalent relief from their reflux symptoms from Nexium, costing \$4.76-\$4.96 per pill, as they would from over-the-counter Prilosec, costing \$0.67 per pill (and perhaps also avoid the expense and time required for a doctor visit to obtain the prescription for Nexium).

9. Furthermore, if it were clinically important to suppress stomach acid for a longer period of time, the difference between a single daily dose of Nexium 40 mg working for 14.0 hours compared to a single dose of Prilosec working for 11.8 would be irrelevant. The reasonable conclusion would be that the clinically superior strategy would be to give Prilosec 20 mg twice daily, costing \$1.34 per day, or Nexium 20 mg twice daily, costing \$9.92 per day).

10. Through its massive false advertising campaign, AstraZeneca persuaded Prilosec patients and their physicians that the “New Purple Pill,” Nexium, was better and more effective than Prilosec in treating heartburn. Thus, Nexium became the most heavily marketed drug in America. The media was blanketed with Nexium ads – “Today’s Purple Pill is Nexium, from the makers of Prilosec.” To encourage and entice patients and physicians to switch to Nexium, AstraZeneca originally priced Nexium below Prilosec, gave deep discounts to managed care plans and hospitals, bombarded doctors with free samples because AstraZeneca knew that frequently doctors prescribe those medicines that they can give to patients as free samples, and even offered coupons in newspapers. AstraZeneca’s six thousand strong sales force flooded physician offices and induced doctors to prescribe Nexium with spurious data proclaiming Nexium’s superiority to omeprazole, which was now available as a generic. The promotional

⁵ Amrstrong D, Talley NJ, Lauristen K, et al. The Rolw of Acid Suppression in Patients with Endoscopy-Negative Reflux Disease: The effect of Treatment with Esomeprazole or omeprazole. *Alimentary Pharmacology & Therapeutics*. 2004; 20: 413-421.

campaign reportedly cost AstraZeneca a half-billion dollars in just 2001. Practically overnight, the “New Purple Pill,” Nexium, began to replace Prilosec for brand name recognition as the heartburn medicine of choice by the public and physicians. Soon the company dropped all reference to Prilosec in its advertisements in an orchestrated effort to make people forget about Prilosec. Now, they just refer to “the purple pill called Nexium.” It’s as though Prilosec never happened. Most physicians and clearly the general public do *not* know that the “New Purple Pill,” esomeprazole or Nexium, is nothing more than the S-isomer of omeprazole. Thus, AstraZeneca’s subterfuge was very successful. Practically speaking, Nexium is “exactly the same as” half of Prilosec, which explains why they no longer refer to Nexium as the “New Purple Pill.” AstraZeneca now refers to Nexium as just the “Purple Pill.”

11. To capture the market, it originally sold Nexium at prices below that of Prilosec. After Nexium was accepted by doctors and consumers, AstraZeneca raised the price to roughly \$4 per pill. Prilosec sells for \$0.46 per pill. One particularly striking example of “underpricing” to get into Nexium into use was described by the BOSTON GLOBE in 2002:

“In exchange for getting Nexium at a fantastic discount, the hospitals [Brigham and Women’s and Massachusetts General Hospital] agreed to make it their primary PPI. The switch will save Mass. General alone more than \$300,000 a year. And the price discount is clearly worth it for AstraZeneca, since patients will be discharged on Nexium, residents will be trained on Nexium, and doctors across the country will be told that Nexium is the first choice of world-famous Mass. General.”⁶

12. AstraZeneca’s campaign worked, while sales of Prilosec fell in response to generic competition, sales of Nexium sky rocketed to reach \$3.3 billion by 2003.

13. AstraZeneca’s Nexium promotional and advertising campaign has resulted in billions of dollars of unnecessary drug expenditures at a time when the rising cost of American health care is creating a crisis and drug costs are the most rapidly increasing component of the health care system. AstraZeneca justified Nexium’s superiority and effectiveness based on its

⁶ Neil Swidey, *The Costly Case of the Purple Pill*, BOSTON GLOBE, November 17, 2002.

own previously noted clinical studies comparing 40 mg of Nexium to 20 mg of Prilosec. The findings from these studies were then used by AstraZeneca to proclaim Nexium's effectiveness. But a dose of 40 mg is not needed in most patients. A MEDLINE search for studies comparing 20 mg of Nexium and Prilosec revealed two published studies, both sponsored by AstraZeneca and both measured relief of symptoms from heartburn and esophagitis. One study (already mentioned above) showed no advantage of Nexium 20 or 40 mg over Prilosec 20 mg in patients with endoscopy-negative esophagitis symptoms (*i.e.*: absolutely no advantage for Nexium).⁷ The other study, which included people with endoscopy-positive esophagitis, declared Nexium the winner:

CONCLUSION: Esomeprazole [Nexium] was more effective than omeprazole [Prilosec] in healing and symptom resolution in GERD patients with reflux oesophagitis, and had a tolerability profile comparable to that of omeprazole.

Nexium 20 mg may have been more effective than Prilosec 20 mg from a statistical point of view, but from a clinical point of view the difference was miniscule: Patients taking Nexium averaged relief one day sooner (seven vs. eight days) and at the end of eight weeks 3% more of the patients taking Nexium 20 mg had resolution of esophagitis than those taking Prilosec 20 mg (89.9% vs. 86.9 %, respectively). And this advantage was cancelled out by the 3.1% greater frequency of adverse events that occurred in those taking Nexium 20 mg compared to those taking Prilosec 20 mg. This data hardly supports the idea that people should be spending \$4.96 per pill for Nexium 20 mg when they could be getting Prilosec 20 mg without a prescription for \$0.67 per pill (if, of course, there were no shortage of OTC Prilosec). As a result of this misleading campaign, hundreds of thousands of patients have taken Nexium and continue to do so when there is, in fact, no advantage over Prilosec, and billions of dollars in unnecessary prescription costs have been paid.

⁷ Armstrong, *op. cit.*

14. Recently, the former administrator of the federal Centers for Medicare and Medicaid services (“CMS”), Thomas Scully, stated to a convention of the American Medical Association: “You should be embarrassed if you prescribe Nexium because it increases costs with no medical benefits.”⁸ Mr. Scully noted, “[t]he fact is Nexium is Prilosec ... [i]t is the same drug. It is a mirror compound.” Mr. Scully further stated that “*Nexium is a game that is being played on the people who pay for drugs.*” Mr. Scully’s comments are too late — AstraZeneca has succeeded in capturing the market.

15. In this action, Plaintiff and the Class seek restitution and equitable relief arising out of AstraZeneca’s sale and promotion of Nexium pursuant to practices and acts that are unfair, deceptive and unlawful in violation of state laws.

II. PARTIES

16. Plaintiff Linda A. Watters, Commissioner, Offices of Financial and Insurance Services for the State of Michigan in her capacity as Rehabilitator of The Wellness Plan and in her capacity as Liquidator of Michigan Health Maintenance Organization Plans, Inc., formerly known as OmniCare Health Plan, Inc. is a Michigan official whose function is to collect and liquidate all assets and liabilities of the former private third party payers Wellness Plan and OmniCare. At all times relevant to this Complaint, Wellness Plan and OmniCare were private third party payers whose function was to assume the risk of payment of medical and prescription costs on behalf of the participants in its plan. During times relevant to this lawsuit, Wellness Plan and OmniCare paid for prescriptions of Nexium, when they should have only paid for prescriptions for other, comparable, cheaper drugs.

17. Defendant Zeneca, Inc. (“Zeneca”) is a Delaware corporation with its principal place of business at Malvern, Pennsylvania.

18. Defendant AstraZeneca Pharmaceuticals LP is a Delaware limited partnership, with its principal place of business located at 1800 Concord Pike, Wilmington, Delaware.

⁸ NEW YORK TIMES, April 21, 2003.

19. Zeneca, and AstraZeneca Pharmaceuticals LP are collectively referred to as “AstraZeneca.”

20. AstraZeneca maintains research and development and manufacturing facilities worldwide, including in the United States. AstraZeneca reported annual sales of \$18.8 billion in 2003, with an operating profit of \$4.2 billion. Its 2003 sales of Nexium were \$3.3 billion, or 17% of all sales.

III. JURISDICTION AND VENUE

21. This Court has diversity subject-matter jurisdiction over this class action pursuant to the Class action Fairness Act of 2005, which, *inter alia*, amends 28 U.S.C. § 1332 to add a new subsection (d) conferring federal jurisdiction over class actions where, as here, “any member of a class of plaintiffs is a citizen of a State different from any defendant” and the aggregated amount in controversy exceeds five million dollars (\$5,000,000). *See* 28 U.S.C. § 1332(d)(2) and (6). This Court has personal jurisdiction over the parties because Plaintiff and the Class submit to the jurisdiction of the Court and Defendants are both incorporated in Delaware.

22. Venue is proper here in that Defendant is incorporated within the District, the Defendant engaged in substantial conduct relevant to the claims within this District, and Plaintiff suffered substantial loss for purchases of Nexium made within the District.

IV. FACTUAL ALLEGATIONS

A. Prilosec – A Blockbuster Drug for AstraZeneca

23. Prilosec (also known as Losec) is a proton pump inhibitor and according to AstraZeneca’s publicly filed documents by the year 2000 had “set a new global standard in short and long-term treatment of acid related diseases.” According to AstraZeneca’s publicly filed documents, Prilosec had benefited patients in 530 million patient treatments since 1980 and “is

the world's largest selling pharmaceutical." Prilosec was AstraZeneca's most profitable drug with worldwide sales of over \$6 billion by 2000.⁹

24. Patent protection for omeprazole, the active substance in Prilosec, expired in all major markets by the end of 2000 but patent term extensions extended protection until April 2001 in the United States.

25. Omeprazole, the active ingredient in Prilosec, is a "racemic" mixture containing S- and R-enantiomers. Enantiomers are molecules that have two non-superimposable mirror image forms, *i.e.*, a right and left hand version. Racemic mixtures, such as Prilosec, contain equal proportions of the two enantiomers. So, 20 mg of Prilosec (*i.e.*, omeprazole) is really 10 mg of the R-enantiomer and 10 mg of the S-enantiomer.

26. However, in humans, the S-enantiomer of omeprazole is more active than the R-enantiomer, in part due to its better metabolization.

27. With the looming loss of patent protection, AstraZeneca faced the erosion of its number one drug. To put this in perspective, sales of Prilosec of \$5.9 billion in 2000 comprised 39% of AstraZeneca's revenue, with the next drug at 8%. Facing the loss of its most profitable drug, AstraZeneca undertook a series of steps to delay the April 2001 expiration of its patent on Prilosec. Three legal arguments helped to keep the patent on Prilosec in effect until November of 2002, protecting Prilosec sales of \$10 million per day, and more important, providing additional time to switch patients over to Nexium.¹⁰ These three tactics included:

- Arguing that the protective coat put on Prilosec to shield the active contents from degradation by the acidity in the stomach. According to the WALL STREET JOURNAL this is a standard problem that is addressed in standard industry textbooks and products are routinely sold to solve it. A British judge invalidated

⁹ 2001 Annual Report at p. 38.

¹⁰ Gardiner Harris, *AstraZeneca Fends Off Generics for Prilosec ---- New Heartburn Drug Nexium Is Introduced*, WALL STREET JOURNAL, June 6, 2002.

AstraZeneca's claim to a patent on the coating based on its "obviousness," but the case took longer to work its way through US Courts.

- AstraZeneca patented the idea of treating H. Pylori infections with a combination of Prilosec and antibiotics. Therefore, they argued, taking the antibiotics with a generic version of Prilosec would violate their patent.
- AstraZeneca patented a metabolite of Prilosec, a molecule that exists briefly as the body digests omeprazole. AstraZeneca then argued that people taking a generic version of Prilosec would violate its patent by metabolizing the drug into this intermediate chemical for which they held the patent.

Though these tactics are more relevant to discussions of patent law, they are relevant in this case because they gave AstraZeneca more time to accomplish its primary goal: switching as many people as possible directly from its blockbuster drug Prilosec to its "new purple pill" Nexium.

B. The Loss of Patent Protection Results in Lower Prices and Reduced Profits

28. For every year from 1995 through 2002, the pharmaceutical industry was the most profitable industry in the United States, although its profitability declined somewhat in 2002. In 2003, drug companies ranked as the third most profitable industry (14.3%), with mining, crude-oil production the most profitable industry (20.1%) and commercial banks the second most profitable (18.6%). Drug companies were more than three times as profitable as the median for all Fortune 500 companies in 2003 (14.3% compared to 4.6%).¹¹

29. The most profitable drugs are brand name drugs. Brand name drugs typically sell at three times or more that of a generic drug.

30. A Kaiser Family Foundation report noted certain trends causing price increases all of which are germane to this case:

Prescription Drug Prices¹²

¹¹ Kaiser Family Foundation, *Trends as Indicators in the Charges*, Health Care Marketplace 2004 Update..

¹² Kaiser Family Foundation, *Prescription Drug Trends — A Chartbook Update*, November 2001.

The average price of a prescription continues to increase, fueled by increases in manufacturer prices for existing drugs and by proportionately higher prices for newer, brand name drugs. Manufacturer price increases in recent years have been higher than in the mid-1990s.

- The overall average retail prescription price was \$45.79 in 2000, more than double the average price in 1990 (\$22.06) (Exhibit 13). Increases in average retail prices reflect both price increases for existing drugs and shifts in use to newer, more expensive medicines.
- The average retail price of a prescription for a brand name drug was more than 3 times that of a generic drug in 2000 (\$65.29 compared to \$19.33). This price differential between average brand and generic prescription prices has increased over time, from slightly less than 2.9 times in 1996 to 3.4 times in 2000 (Exhibit 13).

31. As set forth herein, each of these factors is implicated in this case, as Nexium is a newer drug with a significantly higher price than the equivalent generic.

32. The Kaiser report also noted the increasing promotion of drugs by pharmaceutical manufacturers:

Prescription Drug Promotion

Promotion for prescription drugs by pharmaceutical manufacturers has continued to grow, reaching nearly \$16 billion in 2000. Spending on traditional forms of promotion, such as “detailing” (the personal selling activities of pharmaceutical manufacturer sales representatives, directed mainly at office-based physicians) and “sampling” (leaving drug samples at sales visits), both continue to increase. But growth has been most rapid for a more recent form of promotion, direct-to-consumer (DTC) advertising.

- Total promotional spending by pharmaceutical manufacturers for prescription drugs grew at an average annual rate of 14% from 1996 to 2000, more than a 70% increase in total promotional spending since 1996 (Exhibit 17).
- The average annual growth rate in DTC advertising spending was 33% between 1996 and 2000, compared to a 14% growth rate for total promotional spending during the same period. In 2000, spending for DTC advertising (\$2.5 billion) comprised 16% of total promotional spending, up from 9% in 1996. However, the major expenditures for promoting prescription drugs continue to be detailing (with spending approximately twice that for DTC promotion) and

sampling (which, when valued at retail value, is more than triple the amount of DTC spending) (Exhibit 17).

Spending for television advertising (nearly \$1.6 billion in 2000) has been an increasing proportion of DTC advertising, rising from 13% in 1994 to 64% of total DTC spending in 2000. TV advertising has grown more rapidly than other forms of DTC advertising: the average annual percent increase in TV advertising spending was 88% from 1994-2000, compared to 25% for print and other forms of DTC promotion (Exhibit 18).

C. The AstraZeneca Solution – The New Purple Pill Nexium

33. Faced with the catastrophic loss of sales from its flagship drug, AstraZeneca carefully plotted a new strategy. The plotting was done by members of the “Shark Fin Project,” a secret group of marketers, lawyers and scientists charged with developing a strategy for averting the patent-expiration disaster. The name of the group derives from the dismal shape the sales chart would trace if AstraZeneca did nothing: an inverted V. Eventually the centerpiece of that strategy was the marketing and promotion of the new drug Nexium. Nexium was viewed by several executives as the poorest solution because it was not any better for ordinary heartburn than Prilosec.

34. AstraZeneca’s plan was to promote Nexium as an improvement to Prilosec and to have brand loyalty built before the expiration of Prilosec’s patents. AstraZeneca knew that brand loyalty is critical – once a doctor locks onto a drug for a certain treatment – he/she is unlikely to change. The same is true for the consumer.

35. AstraZeneca sponsored several studies to justify the use of Nexium. The study that it used to obtain FDA approval concluded that Nexium *at twice* the standard dose of Prilosec was *slightly* more effective:

Investigators observed that the time intragastric pH was greater than four during a 24-hour period was longer with **Nexium 40 mg** once daily than standard healing doses for erosive esophagitis of four other branded proton pump inhibitors currently available by prescription in the United States. On day five, intragastric pH was maintained above 4.0 for a mean of 14.0 hours with **Nexium 40 mg**, 12.1 hours with Aciphex 20 mg, 11.8 hours with **Prilosec 20 mg**, 11.5 hours with Prevacid 30 mg, and 10.1 hours with Protonix

40 mg. **Nexium** also provided a significantly higher percentage of patients with an intragastric pH > 4.0 for > 12 hours relative to the other proton pump inhibitors ($p < 0.05$).

Acid suppression is, however, only a “surrogate endpoint,” meaning that it is not of clinical importance in its own right, but a marker presumed to be of importance. Even if duration of suppression of gastric acid secretion were a valid measure upon which to make a clinical decision, these results show that a single dose of Nexium 40 mg (keeping gastric pH above 4 for 14 hours) would hardly be the choice over giving Prilosec 20 mg (keeping gastric pH above 4 for 11.8 hours) twice daily.

36. AstraZeneca had conducted two multi-center, randomized, double-blind, placebo-controlled studies in a total of 717 patients comparing four weeks of treatment of Nexium 20mg or 40mg once daily versus placebo for resolution of heartburn or GERD symptoms. The patients all had at least a six-month history of heartburn episodes, no erosive esophagitis by endoscopy, and had heartburn on at least four of the seven days immediately preceding randomization. Not surprisingly, the percentage of patients that were symptom-free of heartburn was significantly higher in the Nexium groups compared to those groups that received a placebo, or nothing. Thus, the FDA gave AstraZeneca approval to market Nexium, the “New Purple Pill,” for the treatment of heartburn because it worked better than a placebo, NOT because it was better than Prilosec. The only thing that these two studies proved was that the “New Purple Pill” was better than a placebo in the treatment of heartburn, NOT that it was better than omeprazole, or Prilosec. As a matter of fact, when Nexium was compared to omeprazole in three European symptomatic GERD trials, NO significant treatment related differences were seen.

37. Thus, in these three European symptomatic GERD trials, which AstraZeneca had knowledge of (see NEXIUM package insert); Nexium was proven NOT to be better than omeprazole or Prilosec. Yet, defendants marketed and continue to market Nexium as if the “New Purple Pill” is an improvement and better than omeprazole for the treatment of heartburn, which they knew and continue to know is false. AstraZeneca knew that Nexium would NOT be

better than Prilosec for the treatment of heartburn. Thus, with omeprazole available as a generic drug, AstraZeneca had to create and perpetuate the myth that Nexium, the “New Purple Pill,” was somehow better than generic omeprazole, and better than OTC Prilosec, which both sell at a fraction of the cost of Nexium. Thus, to sell Nexium to an unsuspecting public and to a somewhat gullible, if not ignorant (but well wine and dined and not lacking for ball point pens), medical profession, AstraZeneca needed some data, no matter how spurious, to claim that the “New Purple Pill” was and is better than omeprazole. Thus, they conducted four clinical trials, which compared escalating doses of 20mg and 40mg of Nexium to the standard dose of 20mg of omeprazole for the treatment of erosive esophagitis, NOT simple heartburn or symptomatic GERD. These trials were crucial to the marketing strategy. AstraZeneca was desperate to show that the “New Purple Pill” was better than Prilosec.

38. Please note what AstraZeneca did. They chose to study the effects of Nexium versus omeprazole in patients with erosive esophagitis, NOT simple heartburn or symptomatic GERD. Also, AstraZeneca chose to compare escalating doses of Nexium to the standard 20 milligrams (mg) dose of Prilosec. Instead of comparing likely equivalent doses (which would have been no more than 20 and possibly as little as 10 milligrams of Nexium, versus the standard 20-milligram dose of Prilosec) the company used higher doses of Nexium. Thus, they compared 20mg and 40mg of Nexium with 20mg of Prilosec. They escalated the dose of Nexium because they knew that the effect of PPI's is dose dependent or dose-related, yet they only escalated the dose of Nexium, they did NOT escalate the dose of Prilosec. To be fair and objective they should have escalated the dose of Prilosec as well. They even acknowledge the dose dependency of PPI's in the package insert of NEXIUM; “By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40mg and leads to inhibition of gastric acid secretion.” Thus, with the trials designed in their favor with escalating doses of Nexium, one would have expected Nexium to do much better than Prilosec. Yet, in two of the four trials, there was NO

significant difference between Nexium 20mg, Nexium 40mg, and Prilosec 20mg, for the treatment of erosive esophagitis. In the other two trials, Nexium 40mg appeared to offer only a very slight improvement in the healing rates of erosive esophagitis when compared to Prilosec 20mg. In one study, Nexium 20mg was compared to Prilosec 20mg, resulting in a healing rate of 89.9% for Nexium 20mg compared to a healing rate of 86.9% for Prilosec 20mg. This is NOT a *significant improvement in the clinical efficacy* of Nexium over Prilosec. As a matter of fact, in the Medical Review of Nexium, the FDA stated that, “*superiority of NEXIUM over omeprazole was not demonstrated*” in these studies. Furthermore the FDA stated, “*There are no studies which demonstrate that H is superior to O, clinically or even statistically*” (H designates esomeprazole or Nexium and O designates omeprazole or Prilosec). The significant finding in these trials is that Nexium didn’t do better than Prilosec did even at the escalated dose of Nexium 40mg, which is twice the standard dose of Prilosec 20mg. The logical objective conclusion from these studies would have been to simply double the standard dose of Prilosec, allow generic competition, sell Prilosec over-the-counter, and forget about the “New Purple Pill,” but that would not have helped the profit making objective of AstraZeneca.

39. Designing a clinical trial for the treatment of erosive esophagitis in and of itself is not fraudulent or deceptive, but to use the data (healing rates) from those trials to claim that Nexium is better than Prilosec for the treatment of common everyday heartburn or symptomatic GERD, is fraudulent and deceptive, when in fact in those same studies, the data did NOT demonstrate that Nexium 20mg was better than Prilosec 20mg for the resolution of heartburn symptoms. In one of those studies, even the escalated dose of Nexium 40mg was NOT better than Prilosec 20mg for the resolution of heartburn symptoms. Yet, AstraZeneca promoted Nexium to physicians and the public as the “first proton pump inhibitor (PPI) to offer significant clinical improvements over Losec... in terms of acid control and clinical efficacy.” Losec is another name for Prilosec.

40. The FDA's Medical Review of Nexium's new drug application tells a very different story. This FDA's review summarized all of the studies – published or not – submitted with AstraZeneca's NDA for three indications for Nexium: healing of erosive esophagitis (four studies), maintenance of healing of erosive esophagitis (two studies), treatment of symptomatic GERD (gastroesophageal reflux disease) (five studies).¹³ The Medical Review reports that:

“All of these studies were well-designed and apparently well-executed, double-blind, randomized, with appropriate: a) controls; b) patient populations; c) consistent inclusion criteria and reasons for exclusion; and d) sufficient sample size for appropriate statistical power.”

41. So what did these high quality studies show? For healing of erosive esophagitis:

“...a superiority claim of NEXIUM over omeprazole [Prilosec] is NOT SUPPORTED by either the comparison of H20 [Nexium 20 mg] vs. O20 [Prilosec 20 mg] or the comparison of H40 [Nexium 40 mg] vs. H20 [Nexium 20 mg]. [FDA's emphasis]

42. For maintenance of healing of erosive esophagitis: The two studies compared various doses of Nexium to placebo only, not to an active comparator, like Prilosec.

43. For treatment of symptomatic GERD:

“...claims of superiority [of Nexium] to omeprazole are – once again – not supported. Neither H40 [Nexium 40 mg] nor H20 [Nexium 20 mg] could be differentiated from O20 [Prilosec 20 mg].

44. The “SUMMARY OF BENEFITS VS RISKS” section of the FDA's Medical Review of the Nexium new drug application is worth quoting at length:

It is important to point out that in order to determine whether one compound is superior to another, these drugs need to be tested at comparable amounts: H20 [Nexium 20 mg] vs. O 20 [Prilosec 20 mg]; H40 [Nexium 40 mg] vs. O 40 [Prilosec 40 mg]. The sponsor's comparisons of H40 to O 20 do not yield valid conclusions about the superiority of H [Nexium] over O [Prilosec], although these comparisons are adequate to demonstrate that [Nexium] is active in the assessed indications. Therefore the sponsor's conclusions that [Nexium] has been shown to provide a significant clinical advance over [Prilosec] in the first-line

¹³ Hugo E. Gallo-Torrees, MD, PhD, Medical Team Leader, Medical Review(s), FDA Center for Drug Evaluation and Research, Application Number: 21-153/21-154, September 21, 2000. pp 3-6.

treatment of patients with acid-related disorders **is not supported by data.** [Underlining and bold are from FDA report.] ¹⁴

45. And the final conclusion of this report:

In addition, it is recommended not to allow the sponsor to claim that [Nexium] has any significant clinical advantage over [Prilosec] in the first-line treatment of these acid-related disorders because no data in support of such a claim have been submitted.¹⁵

46. Nonetheless, AstraZeneca claimed that Nexium offered “significant clinical improvements over Losec... in terms of acid control and clinical efficacy.” Thus, AstraZeneca claimed that Nexium was significantly more effective than Prilosec for the treatment of heartburn and that it provided relief in a shorter period of time. AstraZeneca repeated this message in a barrage of marketing activities directed to patients (the public) and physicians, and is still promoting this message as outlined in ¶ 7 above.

47. Another deceptive aspect about using erosive esophagitis in a clinical trial to support the use of Nexium for simple heartburn is that erosive esophagitis can only be diagnosed by an invasive procedure called endoscopy. AstraZeneca is shrewd enough to know that a physician is NOT going to perform an endoscopy, and diagnose erosive esophagitis, before writing a prescription for Nexium when a person first complains of heartburn. In other words, most patients who are given a prescription of Nexium, are NOT being treated for erosive esophagitis. Instead, most patients have received Nexium, the “New Purple Pill” for symptomatic GERD or simple heartburn, which AstraZeneca knows is just as effectively treated with omeprazole, or Prilosec. Yet, AstraZeneca used the spurious data from the erosive esophagitis trials to persuade physicians and patients that the “New Purple Pill” should be prescribed over omeprazole for simple heartburn. Due to the effectiveness and power of the massive false Direct-to-Consumer (“DTC”) advertising that AstraZeneca orchestrated, the general public has been indoctrinated to demand the brand name Nexium to treat simple

¹⁴ *Ibid.*, p. 171.

¹⁵ *Ibid.*, p. 174.

heartburn. And the primary care physicians and specialists comply with the demand because they have been misled by the studies with unfair comparisons, continuing education lectures that are dominated by experts with financial ties to drug companies, advertising, and deceptive drug detailing practices of AstraZeneca's drug reps. Thus, instead of prescribing generic omeprazole or OTC Prilosec for simple heartburn, the physician writes a prescription for Nexium. Furthermore, the only acid-related indication for which the dose of Nexium is 40 mg is the healing of erosive gastritis (the recommended dose for maintenance of healing of erosive esophagitis and symptomatic relief of GERD is 20 mg daily). And, the price of 40 mg is actually lower than the price of 20 mg tablets, \$4.76 vs. \$4.96, respectively. One might assume from the emphasis on benefit for the treatment of erosive esophagitis and the curious pricing structure that AstraZeneca were trying to get doctors to prescribe Nexium 40 mg so that the dose would necessitate a prescription and provide a disincentive to switching to OTC Prilosec (when there is no longer a shortage).

48. AstraZeneca did not publish a clinical study of the effectiveness of 20 mg of Nexium versus 20 mg of Prilosec. This study found that Nexium was not more effective than Prilosec.

49. AstraZeneca did not publish the negative study comparing 40 mg of Nexium and 20 mg of Prilosec.

D. The Promotion of Prescription Drugs

50. Promotional spending by pharmaceutical manufacturers has risen steadily in recent years, more than doubling from \$9.2 billion in 1996 to \$19.1 billion in 2001, an average annual increase of 16%. While most promotional spending (86%) remains directed at physicians, a growing proportion is directed at consumers, especially through television ads.

51. Pharmaceutical manufactures use several types of promotion, each of which has been growing in recent years and was employed in this case:

Detailing (29% of spending) is the sales activities of drug representatives directed toward physicians. Most detailing is

directed at office-based physicians (\$4.8 billion), the rest at hospital-based physicians (\$700 million).¹⁶

Sampling (55% of spending) is the free drug samples that pharmaceutical representatives provide to office-based physicians. Sampling, valued at retail pharmacy prices, totaled \$10.5 billion in 2001. Recently, samples are also being made available through DTC advertising venues like TV, newspapers, and the Internet. *Id.*

Direct-to-Consumer (DTC) Advertising (14% of spending) includes advertisements targeted toward consumers through magazines, newspapers, television, radio, and outdoor advertising. *Id.*

Medical Journal Advertising (2% of spending) is the value of professional journal advertisements. *Id.*

52. While DTC advertising remains a relatively small part of overall industry promotion, its rapid spending growth in recent years (increasing an average of 28% annually from 1996-2001), frequent presence on television and in magazines, and extensive use in promoting newer, more expensive medications, have attracted the attention of critics who worry that *it encourages patients to demand high-cost prescriptions for ailments that could be treated effectively with lower cost options.* AstraZeneca's intent was to take advantage of this phenomenon and it succeeded in using its massive Nexium campaign, described below, to encourage consumers to make such demands.

53. A recent study by researchers at the Harvard School of Public Health (M.B. Rosenthal and A.M. Epstein), Massachusetts Institute of Technology (E.R. Berndt), and Harvard Medical School (J.M. Donohue and R.G. Frank) finds that DTC advertising has a significant effect on prescription drug spending. The complete report of their study, *Demand Effects of Recent Changes in Prescription Drug Promotion*, May 29, 2003, can be found at www.kff.org.

54. Significant findings from the study include:

The analysis of advertising and sales growth in the five therapeutic classes studied produces an advertising elasticity of .10, which means that on average a 10% increase in DTC advertising of drugs within a class results in a 1% percent

¹⁶ Kaiser Family Foundation, *Impact of Direct-to-Consumer Advertising on Prescription Drug Spending*, June 2003.

increase in sales of drugs in the class. The study offers the case of proton pump inhibitors (or PPIs, for treatment of ulcers) as an example. Between 1998 and 1999, DTC advertising spending for PPIs increased 60% (from \$49.7 million to \$80.1 million) and PPI sales increased 36% (from \$4.2 billion to \$5.7 billion). Applying the estimated elasticity of .1 to the results for this drug class, the study estimates that \$252 million, or about 17% (or 6 percentage points), of the 36% increase in PPI sales from 1998 to 1999 is attributable to the increase in DTC advertising.

Applying the elasticity to the growth in DTC advertising for the 25 largest therapeutic drug classes, the study estimates that increases in DTC advertising between 1999 and 2000 accounted for 12% of drug sales growth during that period. Applying the 5-class analysis results to the 25 classes with the highest retail spending finds that DTC advertising growth during the year resulted in an additional \$2.6 billion in drug spending in 2000.

DTC advertising is an important, but not the primary, driver of growth in prescription drug spending. However, DTC advertising produces a significant return for the pharmaceutical industry: every additional \$1 the industry spent on DTC advertising in 2000 yielded an additional \$4.20 in sales.

E. A Massive Promotional Campaign and Predatory Price Is Used to Establish Nexium

55. After the sponsored study was concluded, AstraZeneca used the study to promote Nexium as a superior product and launched a massive promotion employing detailing, sampling, and DTC advertising directed at doctors and consumers.

56. For example, in its 2000 Annual Report, AstraZeneca claimed that:

Nexium is the first PPI to offer significant clinical improvements over *Losec* in terms of acid control and clinical efficacy, shown in clinical studies involving over 30,000 patients performed across 20 countries. It is expected to establish a new, improved treatment standard for the PPI class.

Nexium offers more effective acid inhibition than other PPIs and in the treatment of reflux oesophagitis, provides healing and symptom relief in more patients and in a shorter period of time than *Losec*. It is an effective, long-term therapy for GERD patients and can be taken when needed (on demand) to prevent relapse. For the treatment of active duodenal ulcers, seven-day *Nexium* triple therapy (in combination with two antibiotics for the eradication of *Hpylori*) heals most patients without the need for follow-up antisecretory monotherapy.

57. AstraZeneca used these themes in a massive promotional campaign launched to have Nexium replace Prilosec as its flagship drug. AstraZeneca sales representatives spent 2000 and 2001 in a frenzied sales pitch as to the superior qualities of Nexium. And, in the first ten months of 2001 alone, AstraZeneca spent \$98 million on direct-to-consumer promotions, again claiming Nexium was superior to Prilosec. To put the advertising blitz that followed in perspective, the previous record for DTC spending in one year had been set by Vioxx in 2000, spending \$161 million more than what was spent marketing Pepsi or Budweiser beer. In 2002, the first full year that Nexium was on the market, \$183 million was spent on DTC advertising. The following year this increased to \$257 million. Coincident with this enormous amount of advertising, Nexium sales roled 58% in 2003, making it the 7th largest selling drug in the United States.

58. Nexium advertisements directed to physicians claimed that the new drug was more powerful than Prilosec: “we’ve captured the essence of Prilosec and created a new PPI ... introducing Nexium the powerful new PPI from the makers of Prilosec....”

59. To prepare its pitch AstraZeneca flew its entire sales force of 6,000 to Hawaii where they spent an intensive session training on how to pitch Nexium. They were trained to push Nexium even if doctors were resistant or happy with Prilosec. Teleconferences were held whereby the sales force rehearsed the pitch to be made to doctors. In addition its sales force was penalized in their bonuses if they gave away free samples of Prilosec.

60. Its 6,000 person sales force flooded doctors’ offices with free samples and claims of Nexium’s superiority. A July 6, 2002 WALL STREET JOURNAL article depicts one type of pitch made to doctors:

Peter Halper, an internist at a large group practice in Manhattan, has a computer given him by a drug-marketing firm on condition he chat with drug-company marketers via the Internet from time to time. Recently, he checked in with AstraZeneca. The face of a salesman popped onto his screen, asking him how he was and then launching into a pitch for Nexium

Dr. Halper asked the salesman why Nexium was better.

"The proof's in the healing rates," said the live salesman, who cited data comparing 40 mg. of Nexium to 20 mg. of Prilosec. 'We're safer, with no drug-to-drug interactions. We're also the No. 1 proton-pump inhibitor among gastrointestinal specialists.' While he spoke, several graphs flashed on the screen.

'So have I shown you how we differ from the other drugs?' the salesman asked. Dr. Halper said he had. 'Do you need any more samples delivered?' No, Dr. Halper said, he had plenty.

Minutes later, two salesmen from AstraZeneca arrived to talk to Dr. Halper about Nexium. They made sure to restock his cabinet with free Nexium. Since many physicians view Prilosec and Nexium as virtually identical, they often prescribe whichever one is in their free-sample closet. Patients who begin with free samples often continue with paid prescriptions, so the freebies are effective marketing tools.

61. No mention in this pitch was made of the fact that equivalent doses of Nexium was not effective, nor was the claim of "superiority" accurate in that the clinical studies comparing higher doses of Nexium to the standard dose of Prilosec showed just a slight increase in efficacy, and that one of the trials showed no increase in efficacy.

62. AstraZeneca also engaged in a massive advertising campaign directed at consumers. The intent of these advertisements was to cause consumers to want to use Nexium. Studies show that such advertisements are effective in causing patients to pressure doctors into prescribing expensive and marginally helpful new drugs. Doctors find it easier and faster to write the prescription than to explain cheaper alternatives. This is why such direct-to-consumer advertising is prohibited in every other developed country (except New Zealand).

63. The promotional campaign was massive in terms of spending and effort:

To promote **Nexium**, AstraZeneca retained the professional and consumer advertising agencies that handle the **Prilosec** promotion. The professional ad agency of record for **Nexium** is Grey Healthcare Group Inc. (ghgroup.com). Klemtner Advertising Inc., a division of Nelson Communications' Healthcare Resources Group Inc., is the consumer advertising agency of record.

AstraZeneca last year spent \$ 97.9 million on the consumer campaign for **Nexium** through October, placing the product as the third most-promoted prescription drug to consumers during this period. This amount was 84.4% of AstraZeneca's total expenditure for direct-to-consumer advertising in the first 10 months of the

year. The company's direct-to-consumer campaign expenditure for **Nexium** totaled more than the entire consumer advertising efforts in that period for Abbott Laboratories (abbott.com), Eli Lilly & Co. (lilly.com), and Novartis (novartis.com). Nexium was the fourth most-promoted drug in medical journals in 2001, according to Perq/HCI (www.perqhciresearch.com).

64. The effectiveness of such advertising was not lost on AstraZeneca. A Kaiser Family Foundation study found that:

- Nearly a third (30%) of adults have talked to their doctor about a drug they saw advertised, and 44% of those who talked to their doctor received a prescription for the medication they inquired about. This means that one in eight Americans (13%) has received a specific prescription in response to seeing a drug ad.
- After viewing specific prescription drug ads, about four in ten said they were very or somewhat likely to talk to their doctor about the drug they saw advertised (37%) and/or to talk to their doctor about the health condition mentioned in the ad (40%).

65. Millions of patients throughout the United States were exposed to advertisements for Nexium.

66. AstraZeneca also engaged in what would, if Prilosec was manufactured by another company, be predatory pricing in violation of federal and state antitrust law. It offered Nexium at prices below the price of its own Prilosec, hoping that if it established Nexium as a replacement with doctors and consumers, it could later raise the price of Nexium and reap substantial profit after Prilosec's patent had expired.

F. Nexium Is Not More Effective

67. The truth is that there is no evidence that Nexium is superior, at standard doses, to Prilosec and other PPIs:

However, it appears that AstraZeneca, the manufacturer of Prilosec, has been remarkably successful in switching consumers to its newer and more expensive PPI: **Nexium** (esomeprazole), "the purple pill." Sales of omeprazole (both brand name Prilosec and generic) declined from \$4 billion (February 2002 to January 2003) to \$2.9 billion (February 2003 to January 2004), while sales of

Nexium increased from \$2.3 billion to \$3.6 billion for the same time frame. The number of omeprazole (brand name and generic) prescriptions declined from 21.5 million to 17.1 million for those time periods, while the number of *Nexium* prescriptions increased from 15.1 million to 21.3 million, according to NDCHealth.

Drugs for Peptic Ulcers

This is remarkable since there is no evidence that *Nexium* is any more effective than *Prilosec*. The two medications are close chemical relatives. *Prilosec* is made up of two molecules which are mirror images of each other, while *Nexium* is made of one of those same molecules. Clinical trials found that 20 mg or 40 mg of *Nexium* is somewhat more effective than 20 mg of *Prilosec* in healing esophageal erosion. However, no tests were done to compare 40 mg of *Nexium* against 40 mg of *Prilosec*. "Some patients may need 20 mg while some need 40 mg," Dr. Abramowicz says. "When optimal doses are used, *Prilosec* and generic omeprazole appear to be as effective as *Nexium* or any other PPI." (Source: MANAGED HEALTHCARE EXECUTIVE, April 1, 2004.)

68. The situation was described by HEALTH FACTS as follows:

It's tempting to dismiss *Nexium* as just another "me too" drug, one chemical notch away from the other PPIs, and one more example of a pharmaceutical company trying to make us think it has come up with something new. But actually *Nexium* signals a new pharmaceutical industry twist. Normally, a company makes a me-too drug to cut into a competitor's profits, but in this case, both *Prilosec* and *Nexium* are made by the same company. AstraZeneca's reason for competing with its own product is obvious. *Prilosec* (called *Losec* in Canada) will soon go off patent, and generic versions will become available at about two-thirds the cost.

Gone is the pretense that carried the day for Prozac's competitors, who claimed that their me-too antidepressants (*Zoloft*, *Paxil*, etc) had fewer side effects. There is no significant difference in side effects between *Prilosec* and *Nexium*. Both drugs come in delayed-release form, so AstraZeneca has not introduced a new format. In fact, *Nexium* offers no innovation; the drug owes its existence entirely to AstraZeneca's need to retain the company's considerable share of the \$8.3 billion PPI Market.

69. The LOS ANGELES TIMES described the marketing of *Nexium* as follows:

As an example, Cohen compares *Nexium*, the new stomach-acid controller, to *Prilosec*, which is virtually identical and for which a generic is available for a price about 10 times less. But once a patient tries *Nexium* and is doing well, he's not going to want to switch, Cohen says. "Every dollar that goes into these 'me-too'

drugs that are virtually the same as existing drugs is a dollar that is bled out of the health-care system. Drug companies are looking for their profits and will squeeze it every way they can.” (*Source: The LOS ANGELES TIMES, February 15, 2004.*)

70. In 2003, CMS Administrator, Tom Scully, told physicians at a convention of the American Medical Association that they should not prescribe the heartburn treatment Nexium because Prilosec, an older version of the medication that became available in generic form last December, costs less and provides the same level of treatment. Mr. Scully told doctors, “You should be embarrassed if you prescribed Nexium,” because it increases costs with no medical benefits. “The fact is, Nexium is Prilosec,” Mr. Scully said. “It is the same drug. It is a mirror compound.” Mr. Scully said he had no problem paying thousands of dollars a year for an innovative drug that saves lives, like Gleevec, for certain types of leukemia and gastrointestinal tumors. But he said, “*Nexium is a game that is being played on the people who pay for the drugs’ making it one of the most successful launches ever of a new medicine.*”

71. To obtain approval from the U.S. Food and Drug Administration (“FDA”) for Nexium, AstraZeneca had to test it in several clinical trials. Some of these trials merely compared Nexium with placebos to show that it worked better than nothing, since that is all the FDA requires. But four trials compared Nexium head-to-head with Prilosec for esophageal erosions, and these were crucial to AstraZeneca’s marketing strategy. The Company wanted to show that Nexium was better than Prilosec – an advance over the older drug.

72. In total, AstraZeneca submitted 11 efficacy studies and three supportive trials for consideration by the FDA with its NDA for Nexium. See Stephen G. Hundley, *FDA Pharmacology/Toxicology Review and Evaluation*, Nexium NDA 21-154, 1-2 (October 31, 2000) (“FDA Review”). Only *four* of the eleven studies and the three supportive trials actually compared Nexium with omeprazole. The remaining studies compared Nexium with a placebo.

73. Study 172 compared the efficacy of 40 mg Nexium, 20 mg Nexium, and 20 mg omeprazole in healing erosive esophagitis. A sample size of 500 patients per treatment was chosen in order to ensure the ability to detect a 10% difference in healing with 95% accuracy.

Not surprisingly, 40 mg Nexium had a statistically significant higher healing proportion than 20 mg omeprazole, 87.6% versus 81.4%. However, the targeted therapeutic gain of 10% was not reached. In addition, there was no statistically significant difference between 20 mg of Nexium and 20 mg omeprazole according to the FDA reviewer.

74. Study 172 also evaluated 40 mg Nexium, 20 mg Nexium and 20 mg omeprazole for heartburn resolution. The study revealed that there was no significant difference in heartburn resolution between 20 mg Nexium and 20 mg omeprazole. In fact, there was only a statistical difference at week 4, not at week 8, between 40 mg Nexium and 20 mg omeprazole. The study's authors did claim a statistically significant lower number of heartburn free nights with 20 mg of Nexium versus 20 mg omeprazole, but there was no significant difference in heartburn free days and more patients using 20 mg of omeprazole had sustained heartburn resolution by day one of the study.

75. Possibly to remedy the failure to obtain the targeted therapeutic gain of 10% in Study 172, study 173 attempted to reproduce the unremarkable, statistically significant difference between 40 mg of Nexium and 20 mg of omeprazole. This time, however, there was no statistically significant difference between 40 mg Nexium and 20 mg omeprazole. Even at twice the dose, the study "failed to demonstrate the superiority of [Nexium] over[omeprazole]." *FDA Review* at 10. Study 173 did not even attempt to compare 20 mg Nexium and 20 mg omeprazole.

76. AstraZeneca attempted yet again to prove that 40 mg of Nexium was better at healing erosive esophagitis than 20 mg of omeprazole in Study 222. This time, however, over 1000 patients per treatment were used. This number of patients reduced the amount of therapeutic gain required to ensure a 95% accuracy rate from 10% to 5% therapeutic gain. With this lower measure of therapeutic gain, AstraZeneca was finally able to show, within the parameters of the study, that 40 mg of Nexium was more effective than 20 mg of omeprazole.

77. However, the FDA reviewer noted that "the superiority of [40 mg Nexium] over [20 mg omeprazole] was demonstrated by comparing two treatments at different dose level [sic] and does not lead to the conclusion that [Nexium] is superior to omeprazole in healing [erosive esophagitis]." *FDA Review* at 14.

78. Study 174 compared 20 mg Nexium with 20 mg omeprazole. As with Study 172, the FDA reviewer found no statistically significant difference in healing between 20 mg of Nexium and omeprazole. *FDA Review* at 10.

79. Of the three supportive trials submitted by AstraZeneca with the Nexium NDA, one compared 40 mg and 20 mg Nexium with 20 mg omeprazole; one compared 40 mg Nexium and 20 mg omeprazole; and one compared 20 mg Nexium and 20 mg omeprazole. "All three studies failed to demonstrate superiority of [Nexium] over [20 mg omeprazole]." *FDA Review* at 36.

80. The package insert provided with Nexium contains charts summarizing substantially similar study results. The percentage healing rates provided are different in absolute terms than the rates cited by the FDA reviewer, due to the inclusion of different data and/or other variations between the data and samples used, but the overall results are substantially similar to those found by the FDA reviewer. The studies are summarized in the following chart:

EROSIVE ESOPHAGITIS HEALING RATE (LIFE-TABLE ANALYSIS)

Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level*
1	588	NEXIUM 20 mg	68.7%	90.6%	N.S.
	588	Omeprazole 20 mg	69.5%	88.3%	
2	654	NEXIUM 40 mg	75.9%	94.1%	p<0.001 p<0.05
	656	NEXIUM 20 mg	70.5%	89.9%	
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	NEXIUM 40 mg	71.5%	92.2%	N.S.
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1216	NEXIUM 40 mg	81.7%	93.7%	p<0.001
	1209	Omeprazole 20 mg	68.7%	84.2%	

*log-rank test vs. omeprazole 20 mg.

N.S. = not significant (p>0.05).

81. One notable difference between the results cited by the FDA reviewer and those provided in the package insert is that a statistically significant difference is indicated between 20 mg Nexium and 20 mg omeprazole in study 2 in the chart, whereas the FDA reviewer found no statistically significant difference in the equivalent Study, Study 172, between 20 mg Nexium and 20 mg omeprazole. This is because the package insert chart evaluated statistical significance at the .05 level, whereas the FDA reviewer required a more stringent .025 significance level. Furthermore, the difference was only statistically significant at eight weeks, not at four weeks.

82. Another chart provided in the package insert for Nexium purporting to summarize "Sustained Resolution of Heartburn" shows no statistically significant difference between 20 mg Nexium and 20 mg omeprazole in the same study:

SUSTAINED RESOLUTION* OF HEARTBURN (EROSIVE ESOPHAGITIS PATIENTS)

Study	No. of Patients	Treatment Groups	Cumulative Percent# with Sustained Resolution		Significance Level*
			Day 14	Day 28	
1	573	NEXIUM 20 mg	64.3%	72.7%	N.S.
	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	NEXIUM 40 mg	64.8%	74.2%	p<0.001 N.S.
	620	NEXIUM 20 mg	62.9%	70.1%	
	626	Omeprazole 20 mg	56.5%	66.6%	
3	568	NEXIUM 40 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1187	NEXIUM 40 mg	67.6%	75.1%	p<0.001
	1188	Omeprazole 20 mg	62.5%	70.8%	

*Defined as 7 consecutive days with no heartburn reported in daily patient diary.

#Defined as the cumulative proportion of patients who have reached the start of sustained resolution.

*log-rank test vs. omeprazole 20 mg.

N.S. = not significant (p>0.05).

83. An examination of the chemical make-up of Prilosec and Nexium also illuminates the inherent flaws of AstraZeneca's studies supporting its NDA for Nexium.

84. Prilosec (*i.e.*, omeprazole) contains equal proportions of the two enantiomers (R and S). 20 mg of Prilosec is really 10 mg of the Senantiomer. However, in humans, the Senantiomer is more active than the Renantiomer, in part due to its better metabolism. Thus, when faced with the expiration of its patent on Prilosec, AstraZeneca patented just the

S-enantiomer of omeprazole under the name esomeprazole or Nexium. Nexium contains just the S-enantiomer of omeprazole, and therefore, is simply Prilosec without the less active R-enantiomer.

85. Even when comparing equal dose. Nexium has a greater proportion of the more active S-enantiomer than Prilosec. “[A] 20 mg tablet of single-isomer esomeprazole [*i.e.*, Nexium] contains the same amount of active ingredient as a 40 mg tablet of race omeprazole [*i.e.*, Prilosec].” Stephen C. Stinson, *Chiral Drugs*, 78 SCIENT/TECHNOLOGY No. 43, 55-78 (October 23, 2000), available at: <http://pubs.acs.org/cen/coverstory/7843/print/7843scit1.html>. (last visited February 14, 2005).

86. Therefore, even in the one study that showed a slight benefit of 20 mg Nexium over 20 mg Prilosec, the results of which the FDA reviewer found non-significant, AstraZeneca compared essentially non-equivalent doses. According to one clinician, “40 mg esomeprazole vs 20 mg omeprazole is closer to quadruple the dose, not double ... and the 20 mg vs 20 mg study was not a fair comparison of equal doses.” Dr. Barbara Mintzes, Centre for Health Services and Policy Research University of British Columbia, posting on EssentialDrugs.org, June 7, 2002, available at: <http://www.essentialdrugs.org/edrug/archive/200206/msg0016.php>.

87. Surprisingly, despite the greater amount of S-enantiomer in Nexium, Nexium does not work significantly better when comparing equal 20 mg doses of Nexium and Prilosec according to the FDA reviewer. Even though studies show that Nexium has greater bioavailability and controls gastric pH levels better than Prilosec, these differences do not translate into significantly better clinical outcomes.

88. The truth is that there is no evidence that Nexium is superior, at standard doses, to Prilosec and other PPIs:

However, it appears that AstraZeneca, the manufacturer of Prilosec, has been remarkably successful in switching consumers to its newer and more expensive PPI: *Nexium* (esomeprazole), “the purple pill.” Sales of omeprazole (both brand name Prilosec and generic) declined from \$4 billion (February 2002 to January 2003) to \$2.9 billion (February 2003 to January 2004), while sales of

Nexium increased from \$2.3 billion to \$3.6 billion for the same time frame. The number of omeprazole (brand name and generic) prescriptions declined from 21.5 million to 17.1 million for those time periods, while the number of *Nexium* prescriptions increased from 15.1 million to 21.3 million, according to NDCHealth.

Drugs for Peptic Ulcers

This is remarkable since there is no evidence that Nexium is any more effective than Prilosec. The two medications are close chemical relatives. Prilosec is made up of two molecules which are mirror images of each other, while Nexium is made of one of those same molecules. Clinical trials found that 20 mg or 40 mg of Nexium is somewhat more effective than 20 mg of Prilosec in healing esophageal erosion. However, no tests were done to compare 40 mg of Nexium against 40 mg of Prilosec. "Some patients may need 20 mg while some need 40 mg," Dr. Abramowicz says. "When optimal doses are used, Prilosec and generic omeprazole appear to be as effective as Nexium or any other PPI." (Source: MANAGED HEALTHCARE EXECUTIVE, April 1, 2004.)

89. The situation was described by HEALTH FACTS as follows:

It's tempting to dismiss Nexium as just another "me too" drug, one chemical notch away from the other PPIs, and one more example of a pharmaceutical company trying to make us think it has come up with something new. But actually Nexium signals a new pharmaceutical industry twist. Normally, a company makes a me-too drug to cut into a competitor's profits, but in this case, both Prilosec and Nexium are made by the same company. AstraZeneca's reason for competing with its own product is obvious. Prilosec (called Losec in Canada) will soon go off patent, and generic versions will become available at about two-thirds the cost.

Gone is the pretense that carried the day for Prozac's competitors, who claimed that their me-too antidepressants (Zoloft, Paxil, etc) had fewer side effects. There is no significant difference in side effects between Prilosec and Nexium. Both drugs come in delayed-release form, so AstraZeneca has not introduced a new format. In fact, Nexium offers no innovation; the drug owes its existence entirely to AstraZeneca's need to retain the company's considerable share of the \$8.3 billion PPI Market.

90. The LOS ANGELES TIMES described the marketing of Nexium as follows:

As an example, Cohen compares Nexium, the new stomach-acid controller, to **Prilosec**, which is virtually identical and for which a generic is available for a price about 10 times less. But once a patient tries **Nexium** and is doing well, he's not going to want to switch, Cohen says. "Every dollar that goes into these 'me-too'

drugs that are virtually the same as existing drugs is a dollar that is bled out of the health-care system. Drug companies are looking for their profits and will squeeze it every way they can.” (*Source: LOS ANGELES TIMES February 15, 2004.*)

91. The Oregon Health Resources Commission (“OHRC”) released its Update Report on Proton Pump Inhibitors (“PPIs”) in April 2004. The Subcommittee conducted evidence based reviews of six PPIs: Prilosec, Prilosec OTC, Nexium, Prevacid, Protonix, and Aciphex.

92. The Subcommittee compared the six PPIs for esophagitis healing, relief of symptoms or prevention of relapse in adult patients with GERD, finding:

The PPI Subcommittee agrees by consensus that there is no overall clinically significant difference between proton pump inhibitors for esophagitis healing, relief of symptoms or prevention of relapse in adult patients with GERD.

93. The Subcommittee found no evidence to support the use of one PPI over another:

It is the decision of the HRC Proton Pump Inhibitor Subcommittee that the evidence does not demonstrate a clinical difference in efficacy to justify selection of any PPI as clinically superior to the other drugs in the class.

94. The Subcommittee’s findings are facts known to AstraZeneca but omitted from its sales pitches and promotional campaign.

G. AstraZeneca’s Marketing Campaign Has Been Successful: Nexium’s Price is Increased and Sells Billions Per Year

95. Sales of Prilosec have plummeted in response to generic competition. In its 2003 Annual Report, AstraZeneca’s Chief Executive boasted of the transformation from Prilosec to Nexium, trumpeting the \$3.3 billion in Nexium sales achieved in less than three years “after its introduction.”

96. Having established Nexium’s position and capitalizing on brand loyalty, AstraZeneca then raised the price of Nexium. It now sells for \$4.09 per pill versus \$0.46 per pill for Prilosec.

97. A recap of PriLOSEC and Nexium sales reveals the success of Nexium in replacing PriLOSEC:

PRILOSEC VS NEXIUM SALES RECORDS
1998 THROUGH 1st HALF 2004

	WORLDWIDE	U.S.	WORLDWIDE	U.S.
YEAR	PRILOSEC/LOSEC	PRILOSEC	NEXIUM	NEXIUM
1998	4,845,000,000 ¹⁷		--	--
1999	5,909,000,000 ¹⁸		--	--
2000	6,260,000,000 ¹⁹		17,000,000 ²⁰	Launched
2001	5,684,000,000 ²¹	3,694,000,000 ²²	580,000,000 ²³	456,000,000 ²⁴
2002	4,623,000,000 ²⁵	2,847,000,000 ²⁶	1,978,000,000 ²⁷	1,525,000,000 ²⁸
2003	2,565,000,000 ²⁹	867,000,000 ³⁰	3,300,000,000 ³¹	2,477,000,000 ³²
2004	1,071,000,000 ³³	208,000,000 ³⁴	1,826,000,000 ³⁵	1,280,000,000 ³⁶

H. Further examples of Misleading Promotion and Advertising

98. The following Nexium advertisement appeared in print publications:

¹⁷ Source: 2000 Annual Report p. 41.

¹⁸ *Ibid.*

¹⁹ Source: 2000 Annual Report p. 38.

²⁰ Source: 2001 Annual Report p. 7.

²¹ Source: 2001 Annual Report p. 7.

²² Source: 2001 Profit & Loss Statement p. 7.

²³ Source: 2001 Annual Report p. 7.

²⁴ Source: 2001 Annual Report pp. 34, 36.

²⁵ Source: 2002 Annual Report p. 9.

²⁶ Source: 2002 Profit & Loss Statement p. 8.

²⁷ Source: 2002 Annual Report p. 9.

²⁸ Source: 2002 Profit & Loss Statement p. 8.

²⁹ Source: 2003 Annual Report pp. 5, 13.

³⁰ Source: Consolidated Profit & Loss p. 18.

³¹ Source: 2003 Annual Report pp. 1, 13.

³² Source: 2003 Annual Report p. 13.

³³ Source: 2004 Second Quarter Product Sales p. 17.

³⁴ Source: *Ibid.*

³⁵ Source: *Ibid.*

³⁶ Source: *Ibid.*

*Relieve the heartburn.
Heal the damage.
It's possible with the
purple pill called NEXIUM.*



Heartburn is a common problem. It's that uncomfortable burning pain in the upper stomach that spreads to the chest. And that can be serious. If you have heartburn, you could have serious damage to your esophagus (the tube that carries food from your mouth to your stomach).

For heartburn, Nexium gives relief in 1 day. And it can help heal the damage.

For heartburn, Nexium gives relief in 1 day. And it can help heal the damage. Nexium is a powerful medicine that can help heal the damage. Nexium is a powerful medicine that can help heal the damage.

For heartburn, Nexium gives relief in 1 day. And it can help heal the damage. Nexium is a powerful medicine that can help heal the damage. Nexium is a powerful medicine that can help heal the damage.

For heartburn, Nexium gives relief in 1 day. And it can help heal the damage.



99. The foregoing advertisement is misleading and/or deceptive as it fails to disclose that AstraZeneca has manufactured and distributed for sale Nexium solely to maintain the superior profits that derive from sales of a brand name drug, as opposed to a generic drug, and

that AstraZeneca manufactures a far less expensive drug that is equally as effective. The foregoing advertisement is part of an unfair scheme by AstraZeneca to falsely promote and create demand for this product through a combination of promotion to doctors and direct to consumer advertising. The effect of the unfair scheme was to create demand for Nexium where no such demand would have existed at the prices charged for Nexium if AstraZeneca had told the truth about Nexium, and a further effect was to increase the price of Nexium beyond its worth if the truth had been told.

100. The following print advertisement appeared in advertisements:

Bowl of Pasta? Or Bowl of Pain?

It's Different For People with Acid Reflux Disease.

If you've changed your diet, treated the symptoms, but still suffer from persistent heartburn 2 or more days a week, you could have acid reflux disease. And if you do, it can affect everything, from what you eat to how you sleep. But for many people, just one prescription, NEXIUM, a day—combined with sensible diet and lifestyle changes—can mean 24-hour, day and night heartburn relief. Even after meals.

Relieve the heartburn. Heal the damage.



NEXIUM tackles acid reflux at the source. That's important because even a little heartburn, over time, can still mean serious damage to your esophagus. For most people, NEXIUM heals that damage. Your results may vary.

Unlike your stomach, your esophagus offers no protection against churning acid. When acid rises into the esophagus, it can eventually wear away the lining. This condition is called erosive esophagitis and only a doctor can determine if you have it.

NEXIUM works by "turning off" many of the pumps that produce acid. Once the amount of acid has been reduced, NEXIUM can begin to heal any erosions caused by acid reflux disease. Most erosions heal in 4 to 8 weeks with NEXIUM. Your results may vary.

Talk with your health care professional to see if NEXIUM is right for you. NEXIUM has a low occurrence of side effects, including headache, diarrhea and abdominal pain. Symptom relief does not rule out serious stomach conditions.

Don't let acid reflux get in the way.

Relief. Healing. NEXIUM.

Nexium
(esomeprazole magnesium)

For a Free Trial Offer, visit us at purplepill.com or call 1-800-49-NEXIUM

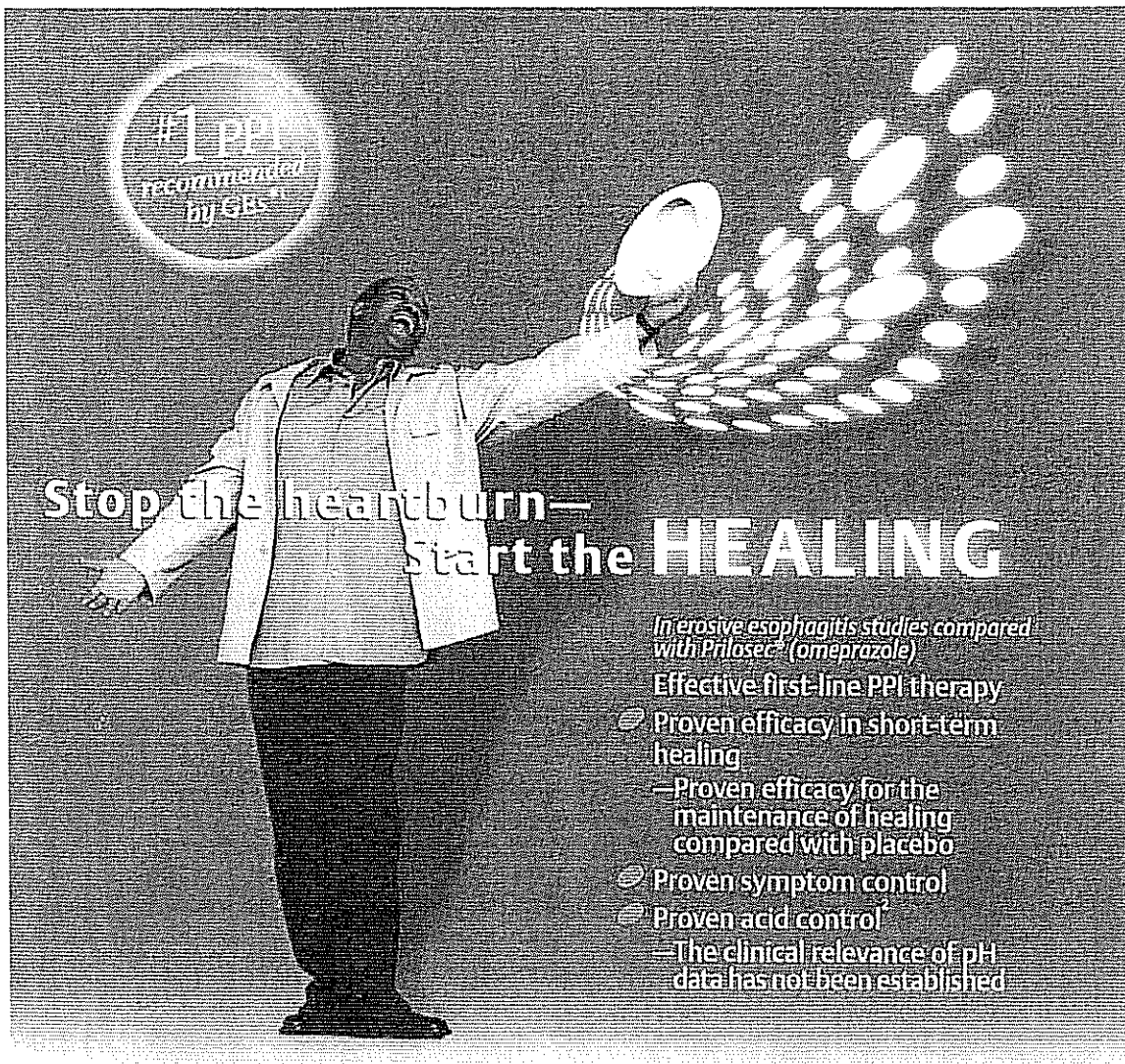
Please read the important Product Information about NEXIUM on the following page and discuss it with your doctor.

AstraZeneca

101. The foregoing advertisement is misleading and/or deceptive as it fails to disclose that AstraZeneca has manufactured and distributed for sale Nexium solely to maintain the profits

that derive from sales of a brand name drug versus a generic drug and that AstraZeneca manufacturers a far less expensive drug that is equally as effective. The foregoing advertisement is part of an unfair scheme by AstraZeneca to falsely promote and create demand for this product through a combination of promotion to doctors and direct to consumer advertising. The effect of the unfair scheme was to create demand for Nexium where no such demand would have existed at the prices charged if AstraZeneca had told the truth about Nexium and a further effect was to increase the price of Nexium beyond its worth if the truth had been told.

102. The following advertisement was published by AstraZeneca:



**Stop the heartburn—
Start the HEALING**

In erosive esophagitis studies compared with Prilosec® (omeprazole)
Effective first-line PPI therapy

- Proven efficacy in short-term healing
- Proven efficacy for the maintenance of healing compared with placebo
- Proven symptom control
- Proven acid control[†]
- The clinical relevance of pH data has not been established

The most frequently reported adverse events with NEXIUM and Prilosec are headache, diarrhea, and abdominal pain. Symptomatic response to therapy does not preclude the presence of gastric malignancy.

NEXIUM and Prilosec should be used only for the conditions, dosages, and durations specified in the full Prescribing Information. Before prescribing NEXIUM or Prilosec, please see brief summary of full Prescribing Information on next page.

[†]Consecutive quarters from October 2001 through December 2002, IMS HEALTH/NDTL

Please visit our Web site at www.Nexium-us.com

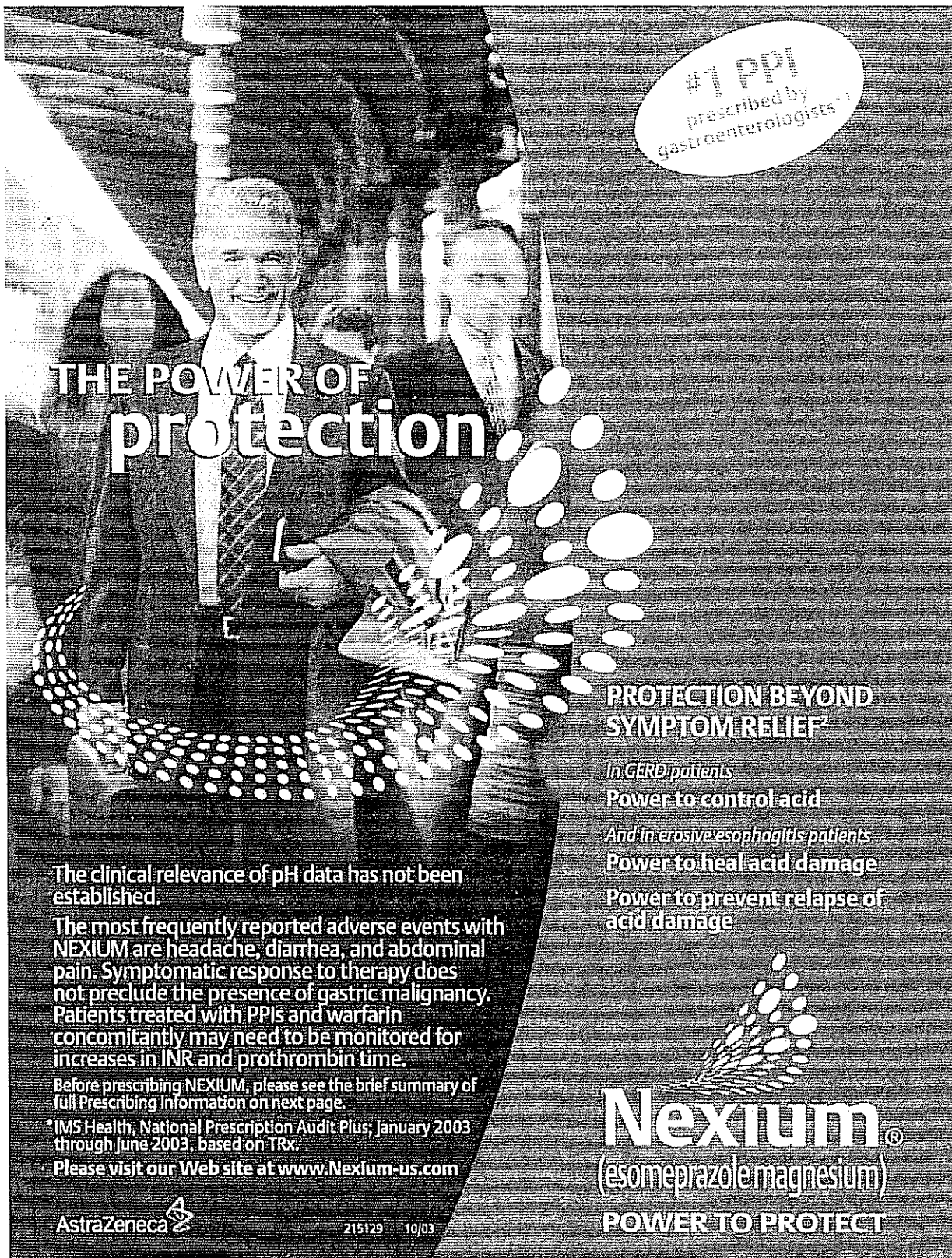
AstraZeneca 



Nexium®
(esomeprazole magnesium)
EXPERIENCE THE POWER

103. The foregoing advertisement is misleading and/or deceptive as it fails to disclose that AstraZeneca has manufactured and distributed for sale Nexium solely to maintain the profits that derive from sales of a brand name drug and that AstraZeneca manufactures a far less expensive drug that is equally as effective. The foregoing advertisement is part of an unfair scheme by AstraZeneca to falsely promote and create demand for this product through a combination of promotion to doctors and direct to consumer advertising. The effect of the unfair scheme was to create demand for Nexium where no such demand would have existed if AstraZeneca had told the truth about Nexium and a further effect was to increase the price of Nexium beyond its worth if the truth had been told.

104. The following advertisement appeared in print:



**THE POWER OF
protection.**

#1 PPI
prescribed by
gastroenterologists^{1,2}

**PROTECTION BEYOND
SYMPTOM RELIEF²**

In GERD patients
Power to control acid

And in erosive esophagitis patients
Power to heal acid damage
**Power to prevent relapse of
acid damage**


The clinical relevance of pH data has not been established.

The most frequently reported adverse events with NEXIUM are headache, diarrhea, and abdominal pain. Symptomatic response to therapy does not preclude the presence of gastric malignancy. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Before prescribing NEXIUM, please see the brief summary of full Prescribing Information on next page.

¹IMS Health, National Prescription Audit Plus; January 2003 through June 2003, based on TRx.

Please visit our Web site at www.Nexium-us.com

AstraZeneca 

215129 10/03

Nexium[®]
(esomeprazole magnesium)
POWER TO PROTECT